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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Application of: Artavanis-Tsakonas *et al.* | Confirmation No.: 8386 |
| Application No.: 10/781,059 | Group Art Unit: 1647 |
| Filed: February 17, 2004 | Examiner: Elly Gerald Stoica |
| For: ACTIVATED FORMS OF NOTCH AND METHODS BASED THEREON | Attorney Docket No.: 7326-132-999 |

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
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Sir:

Applicants hereby request review of the Final Rejection mailed March 26, 2008 ("Final Rejection") of the above-captioned application prior to filing an appeal brief. Applicants submit that the Final Rejection is legally incorrect for failing to accord an effective filing date of the priority date of July 23, 1997 to the subject matter claimed in claim 86. No amendments are being filed with this request. A Notice of Appeal and a Petition for an Extension of Time for three months from June 26, 2008 to September 26, 2008 are submitted herewith.

The present invention relates to methods for identifying modulators of Notch activation. In particular, claim 64 is directed to a method for identifying a modulator of Notch activation comprising contacting a cell with a candidate modulator molecule and detecting or measuring the amount of the expression by the cell of a Notch heterodimer containing a reducing agent-sensitive linkage, in which a difference in the presence or amount of the heterodimer compared to a Notch cell not contacted with the candidate molecule indicates that the molecule modulates Notch activity. Claim 86, which depends from claim 64, recites that the reducing agent-sensitive linkage is a non-covalent, metal ion-dependent sensitive linkage.

In the Final Rejection, the Examiner maintains the position that the subject matter of claim 86 is only entitled to a priority date of July 23, 1998 as its effective filing date, and thus, maintains the rejection of claim 86 as being anticipated by U.S. Patent No. 5,935,792 to Rubin *et*

*al.* ("Rubin") under 35 U.S.C. § 102(e). Applicants disagree and respectfully submit that the subject matter of claim 86 is entitled to a priority date of July 23, 1997 as its effective filing date, and since claim 86 is entitled to such an effective filing date, Rubin is not available as prior art under 35 U.S.C. § 102(e).

The present application is a continuation of U.S. Application No. 09/121,457 filed July 23, 1998 (now U.S. Patent No. 6,692,919), which is a continuation-in-part of U.S. Application No. 08/899,232 filed July 23, 1997 (now U.S. Patent No. 6,436,650). All the presently pending claims, including claim 86, are entitled to the July 23, 1997 filing date since the July 23, 1997 application, No. 08/899,232, fulfills the requirements under 35 U.S.C. § 112, first paragraph, with regard to the pending claims. In particular, claim 86 is entitled to the July 23, 1997 filing date since claim 86 specifies an inherent characteristic of the subject matter that is clearly identified and enabled in Application No. 08/899,232 filed July 23, 1997.

The Patent and Trademark Office ("PTO")'s attention is invited to *Kennecott Corporation v. Kyocera International, Inc.*, 835 F.2d 1419, 5 U.S.P.Q.2d 1194 (Fed. Cir. 1987) and *Application of Nathan*, 328 F.2d 1005, 140 U.S.P.Q. 601 (C.C.P.A. 1964), which collectively stand for the proposition that so long as a product is described and enabled in an earlier patent application, an amendment to the claims of a later-filed application specifying an inherent characteristic of the product, does not deprive the amended claim of entitlement to the earlier application's filing date. As stated by the court in *Kennecott*:

> The disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of an earlier filing date. Nor does the inclusion of a description of that property in later-filed claims change this reasonable result.

*Kennecott* at 1423, 1198.

Claim 86, which depends from claim 64, recites that the reducing agent sensitive linkage of the Notch heterodimer is a non-covalent, metal ion-dependent sensitive linkage. Although the non-covalent, metal-ion dependent nature of the linkage is not explicitly disclosed in Application No. 08/899,232 filed July 23, 1997, the nature of the specific linkage recited in claim 86 is an inherent characteristic of the Notch heterodimer, which heterodimer is sufficiently described and enabled in priority Application No. 08/899,232 filed July 23, 1997.

The PTO's attention is invited to Application No. 08/899,232 as filed at page 9, line 35 to page 10, line 13, wherein it states:

> The present invention is based, at least in part, on the discovery that Notch in its active form, *i.e.*, the form that mediates signal transduction and that binds Notch ligands such as Delta, is a heterodimer of two Notch cleavage products, an about (±10%) 180 kilodaltons (kDa) subunit ($N^{EC}$) and an about

(±10%) 110 kDa subunit ($N^{TM}$), which are tethered together through a reducing agent-sensitive linkage, *e.g.*, one or more disulfide bridges. Full length Notch is not expressed on the cell surface and is ligand inaccessible. As shown by way of example *infra*, the two subunits arise due to a proteolytic cleavage of the full length Notch molecule in the trans-Golgi at a site in Notch amino-terminal to the transmembrane domain and carboxy-terminal to the EGF repeat region, thus generating an extracellular fragment ($N^{EC}$) of about 180 kDa and a transmembrane/intracellular fragment ($N^{TM}$) of about 110 kDa.

The PTO's attention is also invited to the specification at page 19, lines 15-19 of the originally filed specification of Application No. 08/899,232, which states:

> The invention is based, at least in part, on the discovery that the active form of Notch is not the full length form but rather a cell surface expressed heterodimer consisting of $N^{EC}$ and $N^{TM}$ Notch fragments tethered together through a reducing agent-sensitive linkage.

The PTO's attention is also invited to Section 6, in particular Sections 6.3 to 6.10 (pages 45-50), and to Figures 3-7 and 10 of Application No. 08/899,232, which disclose the Notch heterodimer and the two cleavage fragments. In particular, the PTO's attention is invited to Section 6.8 and Figure 6, wherein pulse-labeling experiments are discussed and wherein samples are analyzed that are shown to contain both the $N^{TM}$ and $N^{EC}$. The PTO's attention is also invited to page 53, lines 32-37, which discloses that $N^{TM}$ and $N^{EC}$ are tethered to one another via a linkage that is sensitive to reducing agents. It is indisputable that Application No. 08/899,232 discloses, and that its examples produce, a Notch heterodimer having a non-covalent, metal-ion dependent sensitive linkage, as could be readily determined by one skilled in the art. As but one example, Figure 7 of the 08/899,232 application shows that the Notch heterodimer accumulates on the cell surface, and thus was present in the immunoprecipitate that was produced as described in Section 6.9 on page 49 (by immunoprecipitation with anti-Notch2 antibody PGHN followed by immunoprecipitation with immobilized streptavidin to capture the cell surface molecules that had been labeled with biotin), and subsequently subjected to SDS gel electrophoresis (see, *e.g.*, the sample that was applied to the lane designated 120 min and "S"). Clearly, the Notch heterodimer was also present in, for example, the samples analyzed in Figure 6 (see, *e.g.*, the lanes designated "untreated" in Figure 6A and labeled "37°C" in Figure 6B, at 90 min).

The later-filed, instant Application No. 10/781,059 shows that the Notch heterodimer disclosed and enabled in Application No. 08/899,232 has a linkage that is non-covalent and metal-ion-dependent (see page 52, line 6 to page 53, line 25). These experiments in the instant application analyzed the Notch heterodimer that is recombinantly expressed in S2 cells, which is

the Notch heterodimer in the sample from the recombinant S2 cells of Figure 3E of Application No. 08/899,232 (see lane labeled "S2/N"). Moreover, Application No. 08/899,232 teaches how to obtain such a Notch heterodimer without undue experimentation (see pages 45-50).

Applicants submit that the foregoing demonstrates that the specification of Application No. 08/899,232 fully describes and enables a heterodimeric Notch that has as an inherent characteristic a linkage that is a non-covalent, metal ion-dependent sensitive linkage. Specifying such an inherent characteristic, as does claim 86, does not deprive claim 86 of entitlement to the claimed priority date of July 23, 1997 as its effective filing date. *See, Kennecott Corporation v. Kyocera International, Inc., supra*; *Application of Nathan, supra.* Therefore, claim 86 is entitled to an effective filing date of July 23, 1997.

According to 35 U.S.C. § 102(e), a person shall be entitled to a patent unless "the invention was described in . . . a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, . . .". Further, the 35 U.S.C. § 102(e) date of a reference is the earliest effective U.S. filing date, taking into consideration any proper benefit claims to prior U.S. applications under 35 U.S.C. §§ 119(e) or 120, if the prior application(s) properly supports the subject matter used to make the rejection in compliance with 35 U.S.C. § 112, first paragraph. *See*, MPEP § 706.02(f)(1)(I) and MPEP §§ 2136.02 and 2136.03(III).

Rubin was filed on August 27, 1997 and claims priority to U.S. Provisional Application No. 60/019,390 filed August 29, 1996 and U.S. Provisional Application No. 60/053,476 filed July 23, 1997. In view of the above discussion, Rubin is only available as prior art under 35 U.S.C. § 102(e) against the presently pending claims if, *inter alia*, the subject matter relied on by the Examiner to anticipate the presently pending claims is enabled and described in the August 29, 1996 priority application, since only the August 29, 1996 priority application was filed before the July 23, 1997 effective filing date of the presently pending claims. *See, In re Wertheim*, 191 U.S.P.Q. 90 (C.C.P.A. 1976). As shown by the remarks above, claim 86 is entitled to an effective filing date of July 23, 1997. If the disclosure relied on by the Examiner is only first enabled and described in the July 23, 1997 priority application or in the later filed non-provisional application, filed on August 27, 1997, then Rubin is not available under Section 102(e) because neither application was filed before the July 23, 1997 effective filing date of the presently pending claims.

The PTO's attention is directed to the specification of U.S. Provisional Application No. 60/019,390 filed on August 29, 1996 ("the '390 application") (Ref. A27, of record). Upon review of the '390 application, it is clear that there is no teaching that Kuz proteolytically

cleaves Notch or any disclosure of methods of screening for an agent which modulates the cleavage of a Notch protein by Kuz by detecting or measuring the amount of Notch cleavage products, or any disclosure that Kuz directly interacts with Notch. In view of the foregoing, the subject matter in Rubin relied on by the Examiner is not entitled to the August 29, 1996 priority date. Thus, Rubin is not available as prior art under 35 U.S.C. § 102(e) to the subject matter claimed in claim 86, and cannot anticipate claim 86 as a matter of law.

## CONCLUSION

Applicants respectfully submit that Rubin is not available as a reference under 35 U.S.C. § 102(e) against claim 86 since the subject matter claimed in claim 86 is entitled to an effective filing date of July 23, 1997. Applicants submit that claim 86 meets all requirements for patentability, as has been indicated by the Examiner for pending claims 59-67 and 88, and respectfully request that the Examiner's rejection be withdrawn and that the application be allowed.

Applicants request that the undersigned be contacted at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

Date: September 25, 2008

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